Today, we are CarelonRx, but when we created this document, we were IngenioRx.

Our name may be new, but our commitment to you remains the same.

Drug and Biologic Pipeline Update

Q1 2022

IngenioRx's quarterly *Drug and Biologic Pipeline Update*

Our Q1 2022 edition highlights emerging therapies in the pharmaceutical pipeline. We share insights on a new topical therapy for psoriasis, a first-in-class therapy for Niemann-Pick disease type B, and a new dual mechanism of action agent for Type 2 diabetes. We look at other select significant product approvals, including biosimilars, expected in 2022. In addition, we review future indications being pursued for Dupixent® (dupilumab), a biologic used to treat asthma, atopic dermatitis, and nasal polyps. We report on approvals that originally came to market through the accelerated approval pathway and have been withdrawn by the Food and Drug Administration (FDA). Finally, our market trend section provides a summary of the nonalcoholic steatohepatitis (NASH) pipeline and an overview on uptake of the human papillomavirus (HPV) vaccine.

IngenioRx continues to closely monitor the drug and biologic pipeline and provide this free publication as part of our mission to improve health, reduce waste, lower total cost of care for pharmacy and medical, and estimate future cost impact.

Unless otherwise noted, information contained in this document was obtained from the Centers for Disease Control and Prevention (CDC) (cdc.gov), the FDA (fda.gov), clinicaltrials.gov, releases from pharmaceutical manufacturers, and UpToDate.com (registration required). Information in this document is accurate as of January 25, 2022.

Top emerging new therapies

We expect these products to have significant impact on health plans and members.

ROFLUMILAST

Product:
Roflumilast

Indication:
Treatment of mild-to-severe plaque psoriasis

Estimated FDA approval:
July 2022

Therapeutic class:
Phosphodiesterase type 4 (PDE4) inhibitor

Route of administration:
Topical

FDA designations:
None

Manufacturer:
Arcutis Biotherapeutics

Condition:

Plaque psoriasis affects approximately 80% to 90% of the more than 7 million people with psoriasis in the United States.[1,2] Symptoms can fluctuate, but plaque psoriasis is a chronic inflammatory-driven disease that most frequently results in red, itchy, painful patches of skin, or plaques, in one or more areas of the body.

Role in treatment:

Roflumilast has potential to be the first once-daily, topical, phosphodiesterase type 4 (PDE4) inhibitor for the treatment of adults and adolescents with plaque psoriasis. Guidelines offer recommendations for each of the following FDA-approved topical treatment categories for mild-to-moderate psoriasis as well as adjunctive therapy in more severe disease: steroids, vitamin D analogs, combination steroid/vitamin D analogs, and combination steroid/tazarotene products.[3] The same active ingredient, roflumilast, is already FDA-approved as an oral treatment to reduce risk of exacerbations in people with severe chronic obstructive pulmonary disease (COPD).

Efficacy:

In two phase 3 trials, approximately 1 in 3 to 4 adults with mild, moderate, or severe disease met the primary endpoint of achieving clear or almost-clear skin with roflumilast cream compared to placebo after 8 weeks.

Safety:

Rates of side effects were low and similar between roflumilast and placebo groups. There were no serious treatment-related adverse events.

Financial impact:

With its novel nonsteroidal mechanism of action, once-daily application, and tolerable safety profile, roflumilast could generate additional competition in the topical treatment space. The price is unknown; however, analysts predict peak U.S. sales of $100M to $250M.[4]

IngenioRx view:

While roflumilast cream has submitted an application to the FDA with potential to be the first topical PDE4 inhibitor approved for psoriasis, it is also in late-stage development for atopic dermatitis. In addition to the cream, evaluation of a topical roflumilast foam formulation for the treatment of scalp and body plaque psoriasis, as well as seborrheic dermatitis, is underway. Roflumilast cream and foam will likely join other nonsteroidal topical agents, calcipotriene, calcitriol, and tazarotene, as another topical therapy option to control psoriasis. In the future, updated guidelines will define its place in therapy. It remains unclear if roflumilast will compete with oral agents in moderate-to-severe disease.

OLIPUDASE ALFA

Product:
Olipudase alfa

Indication:
Niemann-Pick disease type B

Estimated FDA approval:
July 2022

Therapeutic class:
Recombinant human acid sphingomyelinase; enzyme replacement therapy

Route of administration:
Intravenous infusion

FDA designations:
Breakthrough, Orphan, Priority

Manufacturer:
Sanofi

Condition:

Niemann-Pick disease (NPD) is a genetic disorder of lipid metabolism. NPD types A and B are caused by a deficiency of the enzyme acid sphingomyelinase (ASM), which is needed to break down lipids, called sphingomyelin. If ASM is absent or not functioning, sphingomyelin accumulates in various organs, including the spleen, liver, lungs, and bone marrow.[5,6]

Signs and symptoms of NPD type B usually develop in preteen years and include enlarged liver and spleen, short stature, impaired lung function, lung infections, and a low blood platelet count. Individuals with NPD type B often survive into adulthood. Symptoms for NPD type A, a more severe form, appear in early infancy, and affected individuals usually do not survive beyond 3 years of age. There are an estimated 1,200 cases of NPD type A and NPD type B worldwide, with the majority being type B.[5,6,7]

Role in treatment:

Current treatment for NPD type B focuses on symptom management. Bone marrow transplantation may be an option in certain individuals.[5] Olipudase alfa would be the first FDA-approved therapy for this condition. It is designed to replace the missing or deficient ASM enzyme.

Efficacy:

The phase 3 ASCEND trial in adults evaluated lung function using the percent predicted diffusing capacity of carbon monoxide (a measure that shows how much oxygen travels from the lungs to the blood). Statistically significant improvement from baseline to week 52 was 22% for olipudase alfa, compared with 3% for placebo. The trial also demonstrated statistically significant positive effects on spleen size. In the olipudase alfa group, spleen volume was reduced by 39.5% compared with a 0.5% increase in the placebo group. Subject-reported outcome measurements evaluating symptoms associated with enlarged spleen did not correlate with the reductions in spleen size. Positive results were also seen in a phase 2 trial in children.[8]

Safety:

Adverse events were mild to moderate compared with placebo in trials. The most common adverse event was infusion site reaction.[8]

Financial impact:

Although the product is expected to be costly, it is unlikely to have a major impact on overall drug spend due to the rarity of the condition.

IngenioRx view:

Olipudase alfa would be the first FDA-approved treatment for NPD type B. Submission has occurred in adults and children, although available data in children is from an unblinded clinical trial.

TIRZEPATIDE

Product:
Tirzepatide

Indication:
Type 2 diabetes

Estimated FDA approval:
May 2022

Therapeutic class:
Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist

Route of administration:
Subcutaneous injection

FDA designations:
None

Manufacturer:
Eli Lilly

Condition:

Diabetes is a chronic condition that affects how the body turns food into energy. Food is broken down into sugar and released into the bloodstream. When this occurs, the pancreas releases the hormone insulin. Insulin allows blood sugar to enter the cells. With Type 1 diabetes, the body does not make insulin. Type 2 diabetes develops when the body does not use insulin properly. Uncontrolled diabetes can lead to long-term health issues, including cardiovascular (CV) disease, kidney disease, nerve damage, and eye damage. An estimated 37 million people in the U.S. have diabetes. About 90% to 95% of them have Type 2 diabetes.[9]

Role in treatment:

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are hormones that stimulate insulin secretion. Tirzepatide acts as an agonist at these receptors. This dual mechanism of action differs from currently marketed therapies that act solely on GLP-1. Similar to GLP-1 agonists, Bydureon BCise® (exenatide extended-release, injection; AstraZeneca), Trulicity®, and Ozempic®, tirzepatide is administered once weekly.

Efficacy:

The SURPASS clinical trial program demonstrated significant improvements in blood sugar control and reductions in body weight for tirzepatide versus placebo, insulin glargine, Tresiba® (insulin degludec, injection; Novo Nordisk) and Ozempic.[10,11] SURPASS-CVOT is a CV outcomes trial that will compare tirzepatide with Trulicity. It is expected to be completed in 2024.[12]

Safety:

The most reported adverse events were gastrointestinal (GI) in nature and mild to moderate in severity. These events increased with dose escalation.[11,13]

Financial impact:

Analysts predict U.S. sales of tirzepatide to exceed $9.7B by 2029.[14] It will compete primarily with the GLP-1 receptor agonist class based on its dual mechanism of action, blood sugar control, and weight loss data reported in clinical trials.

IngenioRx view:

Tirzepatide would be the first GIP receptor agonist FDA-approved for Type 2 diabetes. There will likely be interest in this therapy due to its unique mechanism of action and its clinical trial efficacy data, in particular comparisons with Ozempic. There are concerns with troublesome GI side effects; however, it is possible these could be alleviated by increasing the dose over time.[13] In addition, CV outcomes data evaluating reduction in risk for CV events will not be available for several years. Competing GLP-1 agonists have published CV outcomes. This could limit initial uptake of tirzepatide.

In addition to treatments listed previously, these important drugs and biologics are scheduled to receive Food and Drug Administration (FDA) approval within the next 12 months.

*** * Key**

ABT: add-back therapy

ALS: amyotrophic lateral sclerosis

ESA: erythropoietin stimulating agent

IV: intravenous

PD-1: programmed cell death protein 1

SC: subcutaneous

Orphan drug/rare disease; expected to be high cost but with minimal impact to overall drug/medical spend due to low utilization

Potential to significantly increase overall drug/medical spend

New entrant into high-spend/ trending category

No significant impact to incremental spend due to replacement of existing competitors, based on initial analysis

Other significant product approvals

We expect these products to reach the market in 2022.*

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend
Takecab® (vonoprazan fumarate) Phathom Pharmaceuticals	*Helicobacter pylori* (*H. pylori*) infection/oral	**First in class:** potassium-competitive acid blocker (P-CAB) to be used in combination with anti-infectives for *H. pylori* treatment	3/8/2022	
Relatlimab Bristol Myers Squibb	Melanoma/IV	**First in class:** controls T-cell response, activation, and growth; fixed-dose combination with nivolumab	3/18/2022	
Udenafil AbbVie	Congenital heart disorders in adolescents/oral	**Addition to class:** would be first FDA-approved treatment for this indication	3/26/2022	
Vadadustat Akebia Therapeutics	Anemia in chronic renal disease; dialysis dependent and independent/oral	**Addition to class:** competing to be first oral dosing option to compete with ESAs	3/29/2022	
Toripalimab Coherus BioSciences	Nasopharyngeal cancer/IV	**Addition to class:** would be second PD-1 inhibitor approved for this type of cancer	April 2022	
Ganaxolone Marinus Pharmaceuticals	Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in children and young adults, adjunctive therapy/oral	**Addition to class:** would be first FDA-approved treatment for this indication	4/3/2022	

* As of January 25, 2022.

Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend
Vutrisiran Alnylam	Hereditary transthyretin amyloidosis with polyneuropathy/SC	**Addition to class:** would compete with Onpattro® and Tegsedi®	4/14/2022	
Surufatinib Hutchmed	Neuroendocrine tumors/oral	**Addition to class:** will compete with Afinitor® and Sutent®	4/30/2022	
Tapinarof Roivant Sciences	Psoriasis/topical	**First in class:** will compete with topical treatment options	5/26/2022	
AT-GAA (cipaglucosidase alfa + miglustat) Amicus Therapeutics	Pompe disease/IV + oral	**Addition to class:** IV and oral components coadministered; will compete with Lumizyme® and Nexviazyme®	5/29/2022 (oral); 7/29/2022 (IV)	
Tirzepatide Eli Lilly	Type 2 diabetes/SC	**First in class:** unique dual mechanism of action; will not see cardiovascular outcomes data for several years	5/30/2022	
AMX0035 (taurourso-deoxycholic acid/ sodium phenylbutyrate) Amylyx Pharmaceuticals	Amyotrophic lateral sclerosis/oral	**Addition to class:** may be used in combination with current standard therapy for ALS	6/29/2022	
Tislelizumab BeiGene	Esophageal cancer/IV	**Addition to class:** will compete with other PD-1 inhibitors	7/12/2022	

* As of January 25, 2022.

Other significant product approvals (continued)

Drug or biologic manufacturer	Indication/route**	Place in therapy**	Estimated approval date	Impact on overall drug or medical spend
Roflumilast Arcutis Biotherapeutics	Psoriasis/topical	**Addition to class:** topical cream formulation of roflumilast; will compete with topical treatment options	7/29/2022	
Zynteglo® (betibeglogene autotemcel) bluebird bio	Beta thalassemia/IV	**First in class:** would be first gene therapy approved for treatment of beta-thalassemia; potential safety issues seen in sickle cell disease studies	8/21/2022	
Yselty® (linzagolix) ObsEva	Uterine fibroids/oral	**Addition to class:** will compete with Oriahnn® and Myfembree®; low-dose non-ABT option	9/15/2022	
Ublituximab TG Therapeutics	Multiple sclerosis/IV	**Addition to class:** anti-CD20 monoclonal antibody; one-hour administration time	9/30/2022	

* As of January 25, 2022.

Biosimilar pipeline update

Currently, 32 biosimilars are approved by the Food and Drug Administration (FDA), and 22 have launched in the United States.

Biosimilars are highly similar to their reference product in structure and function; they lack clinically meaningful differences in safety, purity, and potency. Biosimilars may be approved for all or some of the reference product's indications due to patent exclusivity of certain indications. Prescriptions for biosimilars need to be written for the biosimilar by name.

The FDA announced in March 2020 that insulins would be redefined as biologics. This enables them to go through a regulatory pathway that will better facilitate the development and serve as reference products for biosimilars. On June 28, 2021, Semglee®, a biosimilar to Lantus® (insulin glargine), was granted interchangeability status, which would allow the biosimilar to be substituted for the reference insulin without a prescriber's authorization. Cyltezo®, a biosimilar to Humira®, was granted interchangeability status on October 15, 2021, making it the first noninsulin biosimilar to be interchangeable with its reference product.

Biosimilar products in the pipeline or pending launch

Type of benefit	Brand name	Brand manufacturer	Biosimilar name	Biosimilar manufacturer	FDA approval	Launched
Pharmacy	Enbrel®	Amgen	Erelzi®	Sandoz	8/30/16	No
Pharmacy	Enbrel	Amgen	Eticovo™	Samsung	4/25/19	No
Pharmacy	Humira	AbbVie	Amjevita™	Amgen	9/23/16	No
Pharmacy	Humira	AbbVie	Hadlima™	Samsung, Merck	7/23/19	No
Pharmacy	Humira	AbbVie	Cyltezo	Boehringer Ingelheim	8/25/17	No
Pharmacy	Humira	AbbVie	Hulio™	Fujifilm, Mylan	7/6/20	No
Pharmacy	Humira	AbbVie	Hyrimoz®	Sandoz	10/30/18	No
Pharmacy	Humira	AbbVie	Abrilada™	Pfizer	11/15/19	No
Pharmacy	Humira	AbbVie	AVT02	Alvotech, Teva	Pending	No
Pharmacy	Humira	AbbVie	CHS-1420	Coherus BioSciences	Pending	No
Pharmacy	Humira	AbbVie	Yuflyma™ (CT-P17)	Celltrion	Pending	No

Biosimilar pipeline update (continued)

Type of benefit	Brand name	Brand manufacturer	Biosimilar name	Biosimilar manufacturer	FDA approval	Launched
Medical	Avastin®	Genentech, Roche	Bmab-100	Biocon, Mylan	Pending	No
Medical	Avastin	Genentech, Roche	SB8	Samsung, Merck	Pending	No
Medical	Avastin	Genentech, Roche	FKB238	Centus, AstraZeneca	Pending	No
Medical	Avastin	Genentech, Roche	BAT1706	Bio-Thera	Pending	No
Medical	Avastin	Genentech, Roche	BEVZ92	mAbxience	Pending	No
Medical	Avastin	Amgen	CT-P16	Celltrion	Pending	No
Medical	Eylea®	Regeneron	MYL-1701P	Mylan	Pending	No
Medical	Lucentis®	Genentech, Roche	SB11	Samsung Bioepis, Biogen	Pending	No
Medical	Lucentis	Genentech, Roche	FYB201 CHS-201	Coherus BioSciences	Pending	No
Medical	Neupogen®	Amgen	Grastofil®	Apotex, Accord	Pending	No
Medical	Neupogen	Kashiv	Filgrastim	Adello Biologics, Amneal, Kashiv	Pending	No
Medical	Neupogen	Amgen	TX01	Tanvex	Pending	No
Medical	Neulasta®	Amgen	MSB11455	Fresenius, Dr. Reddy	Pending	No
Medical	Neulasta	Amgen	Lapelga Neupeg™	Apotex, Accord	Pending	No
Medical	Neulasta	Amgen	TPI-120	Adello Biologics, Kashiv	Pending	No
Medical	Neulasta	Amgen	Lupifil-P®	Lupin	Pending	No
Medical	Remicade®	Janssen	Ixifi PF™	Pfizer	12/13/17	No

The future of Dupixent

Dupixent® received its first Food and Drug Administration (FDA) approval in 2017 for treatment of adults with moderate-to-severe atopic dermatitis (AD). While use in AD is limited to people who have failed topical prescription therapies, market uptake has been swift and noteworthy. A handful of expanded indications, including younger people with AD, asthma, and nasal polyps, have each contributed to Dupixent's growth with overall global net sales of $1.66B in the third quarter of 2021.

Dupixent is the first biologic that specifically targets interleukin-4 (IL-4) and interleukin-13 (IL-13). It is being evaluated in a variety of type 2 inflammatory-driven diseases. Details outlining 10 new disease states and additional label expansions in Dupixent studies in phase 3, late-stage development and higher, are listed below.

Current and potential Dupixent indications (phase 3)[15,16]

Indications*	Place in therapy*	Estimated future FDA submission dates[17]
Current FDA-approved indications		
Treatment of people 6 years or older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable	First and only biologic FDA approved for AD; competitors in phase 3 development or higher	Approved
Add-on maintenance treatment of people 6 years or older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid-dependent asthma	First IL-4/IL-13 antagonist approved for asthma; competes with Cinqair®, Fasenra®, Nucala, and Xolair®	Approved
Add-on maintenance treatment in adults with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP)	First IL-4/IL-13 antagonist approved for CRSwNP; competes with Nucala and Xolair	Approved
Potential expanded indications		
Potential expansion for treatment of people as young as 6 months of age with moderate-to-severe AD	Would be the first biologic FDA approved for this indication	2022

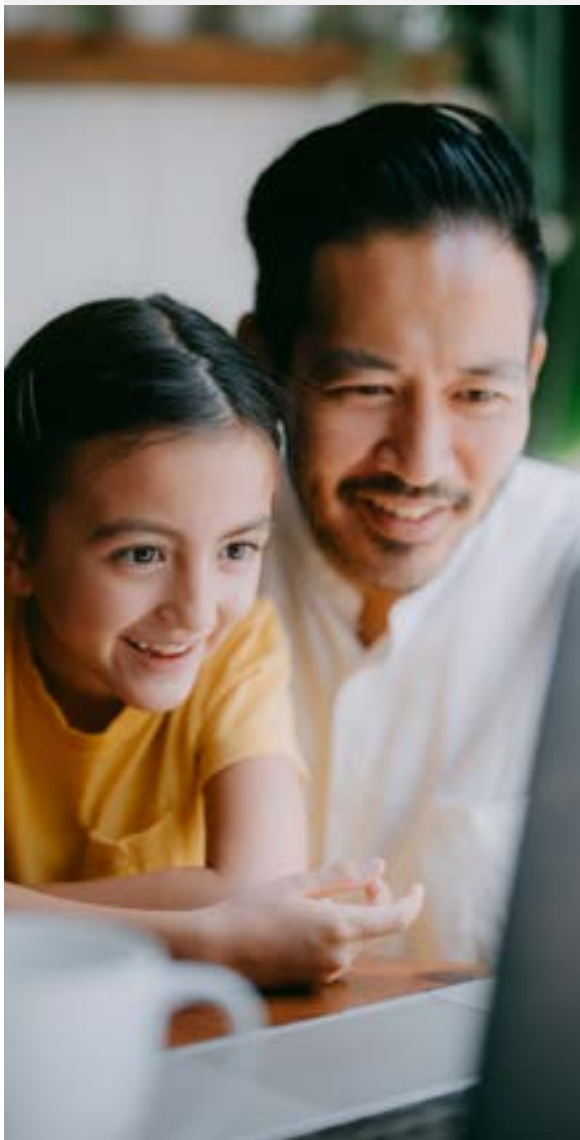
*** Key**

AD: atopic dermatitis

IL-4: interleukin-4

IL-13: interleukin-13

sBLA: supplemental biologics license application



The future of Dupixent (continued)

Indications*	Place in therapy*	Estimated future FDA submission dates[17]
Potential new indications		
Treatment of people 12 years or older with eosinophilic esophagitis (EoE)	Would be the first biologic FDA approved for this indication; also being studied in people 1 to 11 years old	2022
Prurigo nodularis	Would be the first biologic FDA approved for this indication; being studied in adults inadequately controlled on topical prescription therapies	2022
Chronic spontaneous urticaria (CSU)	Would join Xolair as the second biologic approved for people with CSU who remain symptomatic despite treatment with antihistamines; being evaluated in people 6 years or older with moderate-to-severe CSU	2022
Chronic inducible cold urticaria	Would be the first biologic FDA approved for this indication; being studied in people 12 years or older refractory to antihistamines	2022
Chronic obstructive pulmonary disease (COPD)	Would be the first biologic FDA approved for this indication; being studied in adults with COPD, chronic bronchitis, and elevated blood eosinophils	2023
Bullous pemphigoid	Would be the first biologic FDA approved for this indication; being studied in adults	2023
Chronic rhinosinusitis without nasal polyps (CRS without NP)	Would be the first biologic FDA approved for this indication; being studied in people 12 years or older	2023
Allergic fungal rhinosinusitis	Would be the first biologic FDA approved for this indication; being studied in people 6 years or older	2024 and beyond
Allergic bronchopulmonary aspergillosis	Would be the first biologic FDA approved for this indication; being studied in people 12 years or older	Unknown
Hand and foot AD	Would be the first biologic FDA approved for this indication; being studied in people 12 years or older	Unknown

*** Key**

AD: atopic dermatitis

IL-4: interleukin-4

IL-13: interleukin-13

sBLA: supplemental biologics license application

Accelerated approval withdrawals

Since 1992, the Food and Drug Administration (FDA) has used the accelerated approval pathway to bring drugs and biologics to market quicker for diseases or conditions with an unmet medical need. While the traditional pathway requires a well-conducted randomized controlled trial showing positive clinical outcomes (for example, decrease in rates of death or disease exacerbations), the accelerated pathway allows use of surrogate endpoints (for example, laboratory measures or radiographic images) that are hypothesized to predict clinical benefit.[18] Most drugs and biologics approved using the accelerated pathway have oncologic indications.

Key limitations of using surrogate endpoints for approval are not knowing the true benefit of the medication or long-term consequences since the advantage of this approach is a shorter study duration.[19]

Use of the accelerated pathway requires the manufacturer to conduct a confirmatory post-marketing study within a specified time frame to prove a clinical benefit exists. If the benefit is not proven or is not as clinically meaningful as anticipated, the FDA can withdraw or modify the approved indication. The table below provides a summary of drugs or indications withdrawn after failure of confirmatory trials.[18]

*** Key**

AML: acute myeloid leukemia

Chemo: chemotherapy

CLL: chronic lymphocytic leukemia

HER2: human epidermal growth factor receptor 2

LH: luteinizing hormone

MM: multiple myeloma

NHL: non-Hodgkin's lymphoma

NSCLC: non-small cell lung cancer

R/R: relapsed or refractory

SCLC: small cell lung cancer

TNBC: triple negative breast cancer

Drug[20] manufacturer	Accelerated approval indication*	Accelerated approval date	Withdrawal date
	Oncology		
Withdrawn agents			
Zydelig® (idelalisib) Gilead Sciences	Relapsed follicular lymphoma after two or more lines of therapy Relapsed small lymphocytic lymphoma after two or more lines of therapy	7/23/2014	1/14/2022
Copiktra® (duvelisib) Secura Bio	R/R follicular lymphoma after two or more lines of therapy	9/24/2018	12/17/2021
Farydak® (panobinostat) Secura Bio	R/R MM in combination with bortezomib and dexamethasone after two or more lines of therapy	2/23/2015	11/30/2021

Accelerated approval withdrawals (continued)

Drug[20] manufacturer	Accelerated approval indication*	Accelerated approval date	Withdrawal date
	Oncology		
Withdrawn agents			
Pepaxto® (melphalan flufenamide)* Oncopeptides AB	R/R MM in combination with dexamethasone after four or more lines of therapy	2/26/2021	10/22/2021
Lartruvo® (olaratumab) Eli Lilly	Soft tissue sarcoma in combination with doxorubicin	10/19/2016	2/25/2020
Bexxar® (tositumomab and iodine I 131) GlaxoSmithKline	R/R low-grade follicular lymphoma or CD20+ NHL not treated with rituximab	12/22/2004	10/23/2013
Iressa® (gefitinib)** AstraZeneca	Locally advanced or metastatic NSCLC after failure of platinum-based and docetaxel chemo	5/5/2003	4/25/2012
Oforta™ (fludarabine phosphate) Sanofi	R/R B-cell CLL after one or more lines of therapy containing alkylating agent	12/18/2008	12/31/2011
Mylotarg™ (gemtuzumab ozogamicin)** Pfizer	First relapse of CD33+ AML in those 60 or older and ineligible for cytotoxic chemo	5/17/2000	11/28/2011
Withdrawn indications			
Tecentriq® (atezolizumab) Genentech	Unresectable, locally advanced, or metastatic TNBC	3/8/2019	10/6/2021
Istodax® (romidepsin) Celgene	Peripheral T-cell lymphoma after one or more lines of therapy	6/16/2011	7/30/2021
Opdivo® (nivolumab) Bristol Myers Squibb	Hepatocellular carcinoma previously treated with sorafenib	9/22/2017	7/23/2021

Accelerated approval withdrawals (continued)

Drug[20] manufacturer	Accelerated approval indication*	Accelerated approval date	Withdrawal date
Tecentriq (atezolizumab) Genentech	R/R locally advanced or metastatic urothelial carcinoma after platinum-containing chemo or within 12 months of neoadjuvant or adjuvant platinum-containing chemo	5/18/2016	4/13/2021
Keytruda® (pembrolizumab) Merck	R/R metastatic SCLC after platinum-based chemo and one or more lines of therapy	6/17/2019	3/30/2021
Imfinzi® (durvalumab) AstraZeneca	R/R locally advanced or metastatic urothelial carcinoma after platinum-containing chemo or within 12 months of neoadjuvant or adjuvant platinum-containing chemo	5/1/2017	2/19/2021
Opdivo (nivolumab) Bristol Myers Squibb	R/R metastatic SCLC after platinum-based chemo and one or more lines of therapy	8/16/2018	12/29/2020
Celebrex® (celecoxib) GD Searle	Reduce number of adenomatous colorectal polyps in familial adenomatous polyposis	12/23/1999	6/8/2012
Avastin (bevacizumab) Genentech	Chemo-naïve metastatic HER2 negative breast cancer in combination with paclitaxel	2/22/2008	11/18/2011
Ethyol® (amifostine) Clinigen	Reduce cumulative renal toxicity from cisplatin administration in NSCLC	3/15/1996	3/28/2006
	Non-oncology		
Withdrawn agents			
Luveris® (lutropin alpha) EMD Serono	Stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency	10/8/2004	4/12/2016
Withdrawn indications			
Synercid® (dalfopristin/quinupristin) King Pharmaceuticals	Vancomycin-resistant *enterococcus faecium*	9/21/1999	11/12/2010

* Oncopeptides voluntarily withdrew Pepaxto from the market in October 2021 after confirmatory trial showed the drug increased the risk of death. In January 2022, the manufacturer rescinded the letter to the FDA based on further data analysis and is still pursuing full FDA approval.

** New application submitted for separate indication and approved at a later date.

Accelerated approval withdrawals (continued)

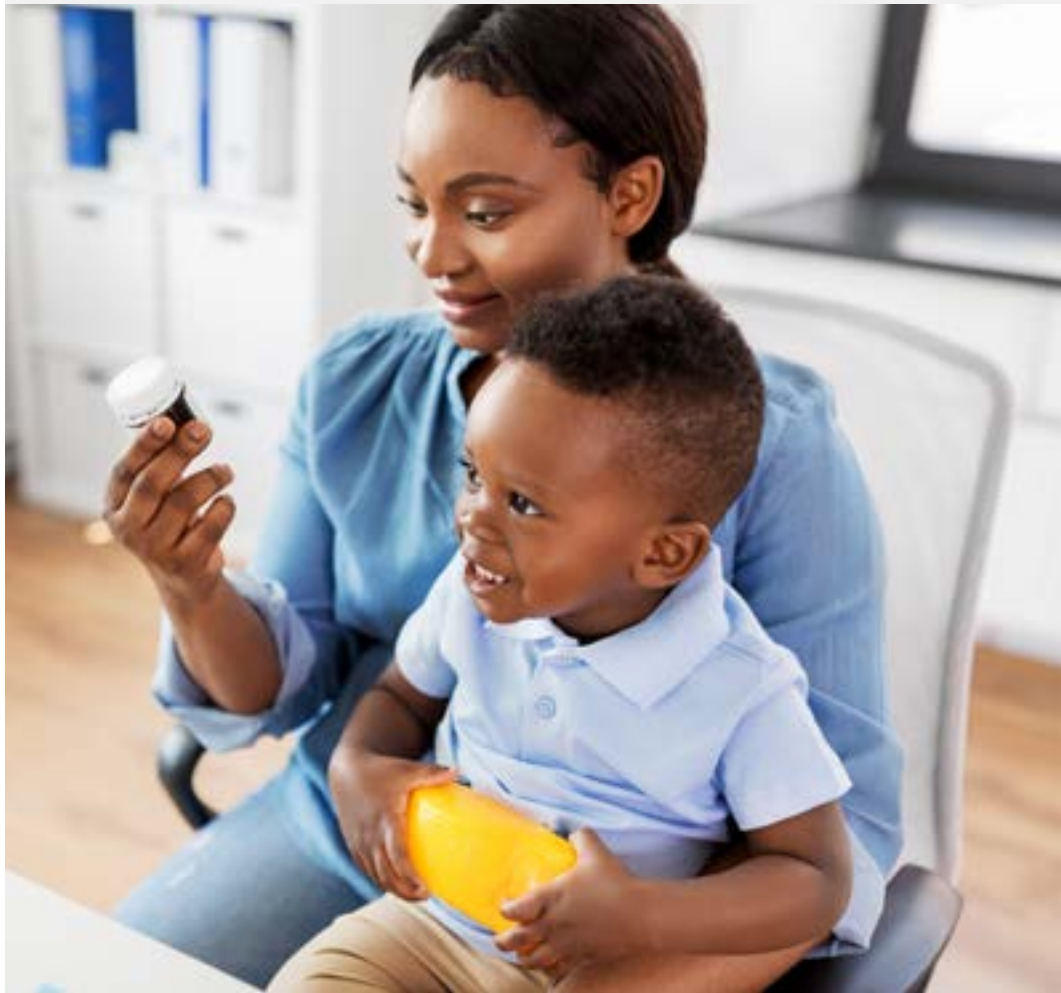
Appropriate use and follow-through of the accelerated approval pathway have recently been in question. Approval of Biogen's Aduhelm® (aducanumab-avwa) for Alzheimer's disease was highly controversial for multiple reasons. Use of the accelerated approval pathway was questioned for basing approval on the surrogate endpoint of reduction in amyloid beta plaque, when clinical outcomes in cognitive impairment did not show a benefit.[21]

In addition, the follow-up with accelerated approvals has been of concern. The FDA Oncologic Drugs Advisory Committee met in April 2021 to review six approvals for which studies failed to confirm clinical benefit, but the agents were still on the market. The committee recommended to maintain four of these six approvals.

These actions prompted the U.S. Department of Health and Human Services Office of Inspector General to launch an examination into the accelerated approval process in 2023. The Institute for Clinical and Economic Review (ICER) and Friends of Cancer Research (FCR) are pushing for changes that will provide greater standardization and transparency in the accelerated approval process.[21]

Success and failure with accelerated approval program[22]

- Withdrawn cancer accelerated approvals = 17
- Cancer accelerated approvals with verified clinical benefit = 83
- Ongoing cancer accelerated approvals = 68
- Average time from accelerated approval to withdrawal = 6.5 years (range: 0.66 to 12.8 years)
- Average time from accelerated approval to verified clinical benefit = 4.1 years (range: 0.18 to 18.1 years)



Market trends

Human papillomavirus vaccination

Recent reports indicate reductions in routine and preventive care, including decreases in human papillomavirus (HPV) vaccination.[26] HPV is a group of viruses often spread through sexual contact. Specific types of HPV can cause genital warts and certain cancers. An estimated 42.5 million Americans are infected with HPV, with more than 13 million new infections yearly. Cancers related to HPV have increased significantly in recent years. In 2015, 43,000 individuals developed an HPV-related cancer, compared to 30,000 in 1999. HPV is associated with more than 90% of cervical cancer cases.[23]

HPV vaccines help protect against infection with HPV. Since 2017, Gardasil® 9 has been the only HPV vaccine available in the United States. The Centers for Disease Control and Prevention (CDC) recommends that HPV vaccination be routinely given to all children and adults ages 9 through 26 years. The vaccine is also FDA approved in ages 27 through 45. The CDC recommends clinicians discuss vaccination with these individuals to determine if it is right for them.[23]

HPV vaccination protects against six kinds of cancer caused by infection with HPV: cervical, anal, back of the throat, penile, vaginal, and vulvar. Safety monitoring has not shown serious adverse events. The most common side effect is dizziness and fainting. However, a recent study demonstrated that more parents are voicing concerns about the safety of HPV vaccines. From 2015 to 2018, the percentage of parents who declined due to safety almost doubled (13% versus 23%). During this same time, reports of serious adverse events after HPV vaccination were rare, at approximately 1.8 per 100,000 HPV vaccine doses, or 0.0018%.[24,25] Concerns are growing that uptake of the vaccine may be even lower now, as early reports during the COVID-19 pandemic showed a marked decline in pediatric vaccine ordering and administration.[26]

Addressing vaccine hesitancy and combating misinformation is important. HPV vaccination, along with screening, has the potential for continued reductions in cervical cancer incidence. Since there is no formal screening for noncervical cancers caused by HPV, vaccination could have a significant impact in these cancers.

Update on the nonalcoholic steatohepatitis pipeline

Anticipation is mounting with the prospect of the first Food and Drug Administration (FDA) approved treatment for nonalcoholic steatohepatitis (NASH), expected in late 2022 to 2023. NASH is a subtype of nonalcoholic fatty liver disease (NAFLD), where there's not only a buildup of excess fat in the liver but also inflammation causing damage. There are seven drugs in phase 3 development for the treatment of NASH. The two closest to FDA submissions are resmetirom, developed by Madrigal Pharmaceuticals, and obeticholic acid (OCA), developed by Intercept.

In 2020, the FDA denied approval of OCA's initial submission for treatment of fibrosis due to NASH. The FDA requested additional clinical data be included with its resubmission to clarify its benefit and safety risks. Intercept recently announced plans to rereview the interim liver biopsy data and review 500 additional biopsies from its pivotal clinical trial to support a resubmission meeting with the FDA in the first half of 2022.

Madrigal announced completing enrollment for its pivotal liver biopsy NASH trial in June 2021, with results likely in the second half of 2022. If positive, these combined with results from another ongoing late-stage resmetirom NAFLD trial could form the basis for a submission in 2022.

Endnotes

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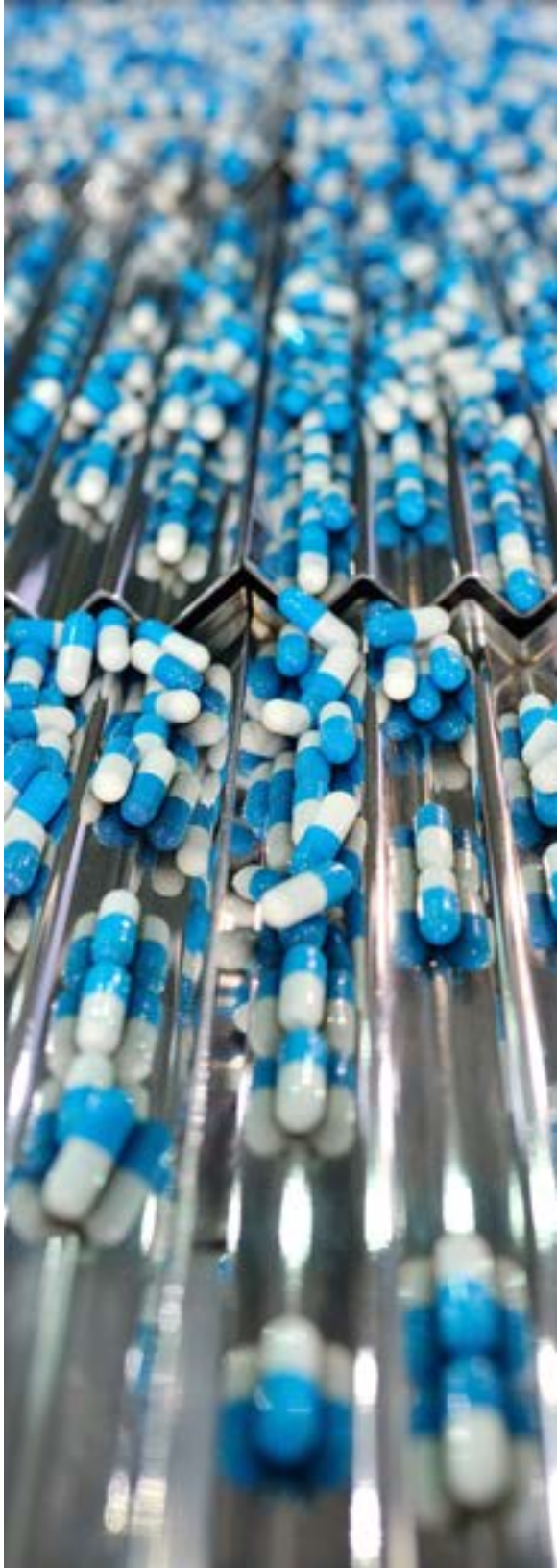

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